UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,049	06/21/2001	Kevin P. Francis	PXE-013.US; 9400-0013	6970

20855 7590 06/13/2005

ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,049	FRANCIS ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-42,45,46 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-33,37-42,45,46 and 59* is/are rejected.

7)☒ Claim(s) *34-36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

8.0.0

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 8, 2004 has been entered.

Claims 19-42, 45, 46 and 59 are pending and under examination in the instant application. Any rejection set forth in the previous Office Action that is not addressed has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the plasmids pAUL-A and pE194 are required to practice the invention. As such, the plasmids must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or

available, a deposit of the plasmids pAUL-A and pE194 may satisfy the requirements of 35 U.S.C. 112, first paragraph. In the instant case, the process to generate the plasmids pAUL-A and pE194 that is disclosed in the specification does not appear to be repeatable, nor does it appear the plasmids are readily available to the public.

> If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

b) all restrictions upon availability to the public will be irrevocably removed upon the granting of the patent;

c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request for the enforceable life of the patent, whichever is longer;

d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

e) the deposit will be replaced if it should ever become inviable.

Failure to make one of the preceding indications in response to this Office Action will result in the rejection being maintained in either a second Non-Final or a Final rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 recites the limitation "said conditional Gram-negative origin of replication" in reference to claim 28. There is insufficient antecedent basis for this limitation in the claim because neither claim 28 nor any claim from which it depends recites the term conditional Gram-negative origin of replication.

Claim 40 recited the term "pSK." The term "pSK" is a trademark, and is therefore subject to change in meaning over time. Because the meaning of the term "pSK" is subject to change, it is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Sohaskey *et al.* (IDS reference AV-1; see entire document; henceforth Sohaskey).

Sohaskey teaches the construction of transposon cassette Tn5353 (see for example Figure 1), present in the plasmid pMAP12 (see for example Figure 4C), which is a derivative of the *Streptomyces* plasmid pIJ702 (see for example Figure 4C, step 9). Transposon cassette Tn5353

comprises inverted repeat (IR) sequences that are functional in the Gram-positive bacteria of *Streptomyces* species, such as *S. coelicor* and *S. fradiae* (see for example the third paragraph on page 367). Within the confines of the IR sequences, Tn5353 comprises an internal coding sequence for a light generating polypeptide (luxA luxB) reporter sequence in a first orientation and a transposon coding sequence (tnpA) in a second orientation (see for example Figure 1). Importantly, the transposon must be operably linked to a promoter element that is functional in *Streptomyces* species, because the transposon must be expressed in order to affect the transposition of the cassette into the host genome, and transposon clearly occurs (see for example the first full paragraph of the left column of page 373 and Figure 5). It is also important to note that Sohaskey describes having obtained transposon cassettes with the luxAB reporter in the same orientation as the tnpA gene, but indicates that this construct produced significantly more light due to the presence of an endogenous transposon promoter for tnpA (see for example the paragraph bridging pages 369 and 371), thus the use of the transposon cassette having the tnpA and luxAB genes in opposing orientations in order to reduce background reporter expression. Plasmid pMAP12 also contains the replicon/origin of replication from plasmid pIJ702 and the selectable *neo* gene (see for example Figure 4C). The pIJ702 origin of replication allows the replication of the cassette in multiple *Streptomyces* species, and therefore is replicable in multiple types of Gram-positive host cells. The *neo* selectable marker confers resistance to the antibiotics *neo*mycin and/or kanamycin (and importantly, can be used for selection in *Streptomyces* species, as well as *E. coli*), and is operably linked to its own promoter in the cassette (see for example the first full paragraph of the right column of page 375). During the construction of Tn5353, Sohaskey describes using strong transcriptional terminator sequences

(T_{fd}) flanking the transposon cassette on both sides (see for example Figures 2 and 3); in other words, Sohaskey teaches the use of at least two transcriptional terminators flanking the transposon cassette in order to prevent transcriptional read-through from the vector construct. Finally, Sohaskey teaches host cells transformed with the cassette, wherein the transposition of the cassette into the genome of the host cell occurs (see for example the first full paragraph of the left column of page 373 and Figure 5). As such, Sohaskey anticipates each of the claims set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46, 59 and 27* are rejected under 35 U.S.C. 103(a) as being unpatentable over Sohaskey (as recited above in the rejection of claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 under 35 USC 102(b)) in view of Birch *et al.* (*J. of General Microbiology* **131**:1299-1303; see entire document; henceforth Birch). Note- * represents those claims specifically rejected by the combination of references.

Sohaskey teaches each of the elements set forth above in the rejection of claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 under 35 USC 102(b). Briefly, Sohaskey teaches a transposon cassette wherein the pIJ702 origin of replication is present in the vector backbone of

the cassette. However, Sohaskey does not teach the use of a temperature sensitive Gram-positive origin of replication with their transposon cassette.

Birch teaches the construction of a temperature sensitive replication mutant for plasmid pIJ702 (see for example the Abstract and the last two paragraphs of page 1301). Birch further teaches that such a temperature sensitive replication mutant could be useful in transposon mutagenesis systems (see for example the last paragraph of page 1301).

It would be obvious to combine the teachings of Sohaskey and Birch because each teaching uses the same vector (pIJ702), and therefore the teachings regarding the vector backbone are analogous. The ordinary skilled artisan would have been motivated to combine the teachings in order to construct a vector having a temperature sensitive origin of replication that Birch explicitly states would be useful for transposon based mutagenesis, which is effectively what Sohaskey is trying to perform in their teachings. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when combining the teachings of Sohaskey with those of Birch to produce a temperature sensitive transposon cassette for mutagenesis of *Streptomyces* species.

Claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46, 59 and 20* are rejected under 35 U.S.C. 103(a) as being unpatentable over Sohaskey (as recited above in the rejection of claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 under 35 USC 102(b)) in view of Schneider *et al.* (US 6,329,160; se entire document; henceforth Schneider). Note- * represents those claims specifically rejected by the combination of references.

Sohaskey teaches each of the elements set forth above in the rejection of claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 under 35 USC 102(b). Specifically, Sohaskey teaches the construction of a transposon cassette wherein a transposase and a "promoterless" luxAB reporter are present in both the opposite and the same orientation within the constraints of the IR sequences of the transposon (see for example the paragraph bridging pages 369 and 371). However, Sohaskey also indicates that this plasmid produced an undesirable level of light, due to the presence of an endogenous transposase promoter that triggered the expression of the luxAB reporter. However, Sohaskey does not explicitly suggest inserting a transcriptional terminator sequence in between the transposase coding sequence and the luxAB reporter encoding sequence to prevent read-through transcription from the endogenous transposase promoter when said sequences are in the same transcriptional orientation.

Schneider teaches the placement of transcriptional termination sequences flanking a luxAB reporter encoding sequence (see for example column 7, lines 14-20). Schneider teaches that the purpose of these terminator sequences is to prevent transcription from promoters outside of the cassette into the lux reporter genes (i.e., to prevent read-through transcription), while those distal to the lux genes assist in preventing the destabilization of the host-vector system" (see for example column 7, lines 23-27).

It would have been obvious to combine the teachings of Sohaskey and Schneider because the teachings of Schneider present a solution to a recognized deficiency in one of the transposon cassettes taught by Sohaskey. Specifically, Schneider teaches a method of preventing the read-through transcription and expression of a luxAB reporter cassette by placing a transcriptional terminator between the reporter and a transposase when both are in the same order. The ordinary

skilled artisan would have been motivated to combine the teachings in order to prevent the read-through of the endogenous transposase promoter into the luxAB reporter cassette, thereby alleviating a recognized deficiency with one of the transposon cassettes described by Sohaskey. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when placing a transcriptional terminator between the transposase and luxAB reporter in the transposon cassette described by Sohaskey as being in the same orientation.

Claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46, 59 and 28*, 29*, 31*, 37* are rejected under 35 U.S.C. 103(a) as being unpatentable over Sohaskey (as recited above in the rejection of claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 under 35 USC 102(b)) in view of Fujiwara *et al.* (US 5,399,496; see entire document; henceforth Fujiwara). Note- * represents those claims specifically rejected by the combination of references.

Sohaskey teaches each of the elements set forth above in the rejection of claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 under 35 USC 102(b). Briefly, Sohaskey teaches a transposon cassette wherein the pIJ702 origin of replication is present in the vector backbone of the cassette, allowing replication to occur in Gram-positive bacteria. However, Sohaskey does not specifically teach including an origin of replication for a Gram-negative host cell on their transposon cassette, although Sohaskey clearly contemplates the need for using Gram-negative hosts in the discussion that the *neo* selectable marker has the advantage of being selected for in a Gram-negative host cell such as *E. coli*, as well (see for example the first full paragraph of page 375 of Sohaskey).

Fujiwara teaches the production of vectors having multiple origins of replication, specifically including an origin of replication for the Gram-negative bacteria, *E. coli* (see for example column 2, lines 44-46). Fujiwara further teaches that *E. coli* is an efficient host for the rapid amplification and manipulation of DNA host vectors (see for example column 2, lines 48-451).

It would have been obvious for the skilled artisan to include a Gram-negative (more specifically, an *E. coli*) origin of replication on the transposon cassettes taught by Sohaskey because the skilled artisan would understand the need to be able to make a continuous amount of the vector for use in the transformation of *Streptomyces* species. Indeed, Sohaskey recognizes the benefits of using a selectable marker that can be selected for in both Gram-positive and Gram-negative cells (such as *E. coli*). The skilled artisan would have been motivated to include a Gram-negative origin of replication on the transposon cassettes of Sohaskey because of the ability to rapidly and efficiently use a Gram-negative host cell (such as *E. coli*) to produce additional quantities of the transposon cassette for the transformation of *Streptomyces*. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when including a Gram-negative origin of replication in the transposon cassettes taught by Sohaskey.

Claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46, 59 and 21* are rejected under 35 U.S.C. 103(a) as being unpatentable over Sohaskey (as recited above in the rejection of claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 under 35 USC 102(b)) in view of Knudtson (as recited in

previous Office Actions). Note- * represents those claims specifically rejected by the combination of references.

Sohaskey teaches each of the elements set forth above in the rejection of claims 19, 22-26, 30, 32, 33, 41, 42, 45, 46 and 59 under 35 USC 102(b). Briefly, Sohaskey teaches a transposon cassette using derivatives of the Tn4556 transposon (i.e., the transposase, resolvase and IR sequences), which originates in the Gram-positive bacterium *S. fradiae*. Sohaskey then teaches the placement of an internal reporter within the transposon cassette, with the reporter in the opposite orientation to the transposase coding sequence, for the purpose of detecting promoter elements. Sohaskey also teaches that, when the reporter cassette is in the same orientation as the transposase coding sequence, an extra*neo*us amount of reporter transcription occurs. However, Sohaskey does not teach using derivatives of the Tn4001 transposon, which originates from a different Gram-positive bacterium, *S. aureus*.

Knudtson teaches the production of a transposon cassette comprising a derivative of the Tn4001 cassette (i.e., the transposase and IR sequences) flanking an internal promoterless reporter cassette, and using the cassette for the purpose of detecting promoter elements. However, Knudtson does not specifically teach placing the internal promoterless reporter cassette in the opposite orientation as the transposase.

It would have been obvious for the ordinary skilled artisan to combine the teachings of Knudtson and the teachings of Sohaskey because they are analogous, where both involve the use of promoterless reporters contained within transposons for the purpose of detecting promoters within the genome of a cell. Indeed, the ordinary skilled artisan would recognize that the principle of placing the transposase encoding sequence and the reporter encoding sequence in

opposite orientation would be equally applicable in any system involving a transposon cassette comprising a promoterless reporter. The ordinary skilled artisan would be motivated to specifically place the internal promoterless cassette taught by Knudtson in the opposite orientation to the transposase also contained within the Tn4001 transposon (thus generating a Tn4001-derived transposon cassette having a transposase in the opposite orientation to a promoterless reporter cassette) because the teachings of Sohaskey indicate that placing a promoterless cassette in the same orientation as a transposase encoding sequence can lead to the production of the reporter gene by the endogenous promoter of the transposase, and this obviously increases the chances of false positives when using a "promoterless" reporter cassette. Thus, it is desirable to have a transposase and promoterless reporter sequence in opposite transcriptional orientations in any transposon cassette comprising a promoterless reporter in order to avoid the inadvertent expression of the reporter by an endogenous transposase promoter, which would result in increased background expression of the reporter. Absent evidence to the contrary, the skilled artisan would have had a reasonable expectation of success when combining the teachings of Knudtson with the teachings of Sohaskey.

Allowable Subject Matter

Claims 34-36 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER